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  *                W E L C O M E   T O   T H E                      *
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  *          U. S.   P A T E N T   T E X T   F I L E                *
*                                                                   *
  * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
* *
L1        1046 PERTUSSIS
L2        3646 TOXIN
L3         198 L1(5A)L2
L4      397888 MUTAT? OR SUBSTITUT? OR MUTAN? OR MUTAGEN?
L5      553561 REPLAC?
L6      805459 L4 OR L5
L7          13 L3(5A)L6
L8          55 (ARG OR ARGININE)(W)9 OR ARG9 OR ARGININE9
L9           1 L8(P)L1
L10          1 L3 AND L8
L11       4149 VACCINE
L12         45 L11(P)L3
L13       1667 (514/12 OR 424/240.1 OR 424/190.1 OR
424/94.5)/CCLS
L14         44 L3 AND L13
L15       1854 (TOXIN/CLM) OR HOLOTOXIN/CLM OR S1/CLM
L16         29 L14 AND L15
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L7          13 L3(5A)L6
1.  5,643,747, Jul. 1, 1997, Genes for the export of pertussis
holotoxin; Steven M. Baker, et al., 435/69.1, 252.3, 252.33,
320.1; 536/23.7 :IMAGE AVAILABLE:

US PAT NO:     5,643,747 :IMAGE AVAILABLE:             L7: 1
of 13
DETDESC:DETD(31)
Identification of B. **pertussis** **toxin** secretion
**mutants**

L12
1.  5,681,570, Oct. 28, 1997, Immunogenic conjugate molecules;
Yan-ping Yang, et al., 424/197.11, 203.1, 234.1, 244.1, 256.1;
514/54; 536/123.1 :IMAGE AVAILABLE:

2.  5,679,784, Oct. 21, 1997, Recombinant mutants for inducing
specific immune responses; Daniel Ladant, et al., 536/23.7;
424/184.1, 240.1; 435/69.3, 252.3, 320.1 :IMAGE AVAILABLE:

3.  5,667,787, Sep. 16, 1997, Purification of a pertussis
outer membrane protein; Gail Jackson, et al., 424/253.1,
254.1; 530/412, 414, 416, 417, 418 :IMAGE AVAILABLE:

4.  5,648,080, Jul. 15, 1997, Antigenic preparations and
isolation of such preparations; Pavel Novotny, 424/254.1,
184.1, 240.1, 253.1; 530/350, 388.2 :IMAGE AVAILABLE:

5.  5,643,753, Jul. 1, 1997, Use of autologous promoters to
express gene products in bordetella; Sheena Loosmore, et al.,
435/69.3; 424/93.4, 235.1, 240.1, 253.1, 254.1; 435/91.1,
91.4, 91.41, 172.3, 252.3, 320.1; 536/23.7; 935/10, 12, 29,
41, 56, 72 :IMAGE AVAILABLE:

US PAT NO:     5,681,570 :IMAGE AVAILABLE:            L12: 1
of 45
DETDESC: DETD(102)
6. Schneerson, R., L. Levi, J. B. Robibin, D. M. Bryla, G.
Schiffman, and  T. Lagergard. 1992. Synthesis of a conjugate
**vaccine** composed of  pneumococcus type 14 capsular
polysaccharide bound to **pertussis**  **toxin**. Infect.
Immun. 60:3528-3532.

US PAT NO:     5,679,784 :IMAGE AVAILABLE:            L12: 2
of 45
DETDESC: DETD(34)
B. **pertussis** AC **toxin** is used to present epitopes of
vaccinal importance to the immune system. This recombinant
toxin may be used as a component of the **vaccine**, either
```

alone or in the presence of other antigenic preparation(s). It can be used in toxic form or in detoxified. . .

US PAT NO: 5,667,787 :IMAGE AVAILABLE: L12: 3 of 45
SUMMARY: BSUM(5)
This . . . hampered by a lack of information on the mechanism of pathogenesis of B. pertussis. Many virulence associated factors, such as **pertussis** **toxin** (PT), also known as lymphocytosis promoting factor (LPF), filamentous haemagglutinin (FHA), adenylate cyclase, lipopolysaccharide, agglutinogens and other outer membrane proteins have been suggested for inclusion in an "acellular" **vaccine**, which is less defined than the component **vaccine**. Much of the work on acellular vaccines has concentrated on a PT-based **vaccine**. Results of a recent clinical trial have indicated that a **vaccine** consisting entirely of PT-toxoid only partially protected children from the infection. A PT/FHA combination showed slightly higher efficacy but this was still lower than .that obtained for the whole-cell **vaccine**.

CLAIMS:
3. The **vaccine** claimed in claim 2, wherein said at least one other purified immunoprotective pertussis antigen is selected from the group consisting of purified **pertussis** **toxin** (PT), purified filamentous haemagglutinin (FHA) and purified agglutinogens.

9. The method of claim 8 wherein the **vaccine** further comprises, as at least one additional component thereof, at least one other purified antigen of Bordetella pertussis selected from the group consisting of purified **pertussis** **toxin** (PT), purified filamentous haemagglutinin (FHA) and purified agglutinogens.

10. A component **vaccine** against disease caused by infection by Bordetella pertussis, which comprises: as a first component, purified pertactin having no detectable adenylate cyclase activity, as an additional component, at least one other purified B. pertussis antigen selected from the group consisting of **pertussis** **toxin** (PT), filamentous haemagglutinin (FHA) and agglutinogens; and a pharmacologically acceptable carrier therefor.

US PAT NO: 5,648,080 :IMAGE AVAILABLE: L12: 4 of 45
SUMMARY: BSUM(4)
The search for a safer, effectively acellular B. pertussis **vaccine** has been hampered in the past by the paucity of information regarding the identity and mechanisms of action of the. . . J. Am. Med. Soc., 248 (1) 22-23). Examples of antigens that have been suggested for investigation include lymphocytosis promoting factor (**pertussis** **toxin**/LPF) filamentous haemagglutinin (FHA), lipopolysaccharide (LPS), agglutinogens, dermonecrotic toxin (DNT), heat labile and heat stable toxins, polymorphonuclear leukocyte inhibitor factor, adenylate cyclase and other surface components (Pertussis **Vaccine** Workshop, Feb. 11, 1982, Bureau of Biologics, U.S.A.). Other proposed candidate antigens for investigation include tracheal cytotoxin and various outer. . .

BSUM(7)
Much of the work carried out on acellular pertussis vaccines is concentrated on the possibility of basing such a **vaccine** on LPF. However, it is believed that most (if not all) of the adverse effects hitherto observed to be associated with **pertussis** vaccination are related to the **toxin**. In combination with tetanus or diphtheria toxoid and LPS, it is able to induce experimental encephalopathy in susceptible mice (L.. . .

US PAT NO: 5,643,753 :IMAGE AVAILABLE: L12: 5 of 45
SUMMARY: BSUM(4)
The . . . whooping cough with the former generating more severe symptoms. The disease, or vaccination against the disease (using an inactivated whole-cell **vaccine**), elicits antibodies against several antigens, typically **pertussis** **toxin** (PT), filamentous haemagglutinin (FHA), agglutinogens or fimbriae and the 69 kDa outer membrane protein or pertactin. These proteins represent the major immunogens that may be included, individually or in combination, in any **vaccine** used to protect against the disease, whether it be the inactivated whole-cell **vaccine** or a defined component **vaccine**. Therefore, the efficient expression of these antigens from the **vaccine** strain is crucial.

BSUM(7)
The . . . vaccines has resulted in a massive reduction in the incidence of whooping cough since their introduction in the 1950s. These **vaccine** preparations are efficacious but have been known for many years to be reactogenic and to be associated with local and. . . are at various stages of clinical assessment in other countries. Defined pertussis vaccines consist of several combinations of the B. **pertussis**-specific antigens **pertussis** **toxin** (PT), filamentous hemagglutinin (FHA), the 69 kDa outer membrane protein (pertactin) and fimbrial agglutinogens. Replacing whole-cell whooping cough vaccines with the defined acellular

preparations has resulted in a substantial increase in the complexity and cost of **vaccine** manufacture. A major portion of these increased costs is due to the relatively low levels of PT and pertactin produced. . .

L16
1. 5,643,753, Jul. 1, 1997, Use of autologous promoters to express gene products in bordetella; Sheena Loosmore, et al., 435/69.3; 424/93.4, 235.1, **240.1**, 253.1, 254.1; 435/91.1, 91.4, 91.41, 172.3, 252.3, 320.1; 536/23.7; 935/10, 12, 29, 41, 56, 72 :IMAGE AVAILABLE:

US PAT NO: 5,643,753 :IMAGE AVAILABLE: L16: 1 of 29
US-CL-CURRENT: 435/69.3; 424/93.4, 235.1, **240.1**, 253.1, 254.1; 435/91.1, 91.4, 91.41, 172.3, 252.3, 320.1; 536/23.7; 935/10, 12, 29, 41, 56, 72

SUMMARY: BSUM(4)
The . . . severe symptoms. The disease, or vaccination against the disease (using an inactivated whole-cell vaccine), elicits antibodies against several antigens, typically **pertussis** **toxin** (PT), filamentous haemagglutinin (FHA), agglutinogens or fimbriae and the 69 kDa outer membrane protein or pertactin. These proteins represent the. . .

BSUM(6)
Along with other genes, the **pertussis** **toxin** operon (TOX), the filamentous haemagglutinin operon (FHA), and the pertactin gene (PRN) are all positively regulated by the Bordetella virulence.

BSUM(7)
The . . . are at various stages of clinical assessment in other countries. Defined pertussis vaccines consist of several combinations of the B. **pertussis**-specific antigens **pertussis** **toxin** (PT), filamentous hemagglutinin (FHA), the 69 kDa outer membrane protein (pertactin) and fimbrial agglutinogens. Replacing whole-cell whooping cough vaccines with. . .

DETDESC: DETD(18)
A pUC-based plasmid (S-3680-10) was constructed which contains the FHA promoter directing the expression of the native **pertussis** **toxin** structural gene and surrounded by the TOX flanking regions (FIG. 1). The FHA promoter is an EcoR I/Hinf I fragment. . .

DETD(64)
TABLE 1

Production of **pertussis** **toxin** (PT), filamentous hemagglutinin (FHA) and pertactin, from Bordetella pertussis strains that contain hybrid prn alleles at the prn locus. The. . .

CLAIMS:
What . . . a Bordetella gene fused at the ATG start codon to an autologous Bordetella promoter, wherein: (a) said promoter is the **pertussis** **toxin** operon (TOXp) promoter and the Bordetella gene is selected from the group consisting of the filamentous haemagglutinin operon (FHA) and. . . said promoter is the filamentous haemagglutinin operon (FHAp) promoter and the Bordetella gene is selected from the group consisting of **pertussis** **toxin** operon (TOX) and pertactin (PRN) gene.

3. . . . gene fused at an ATG start codon to its own native Bordetella promoter, wherein: (a) said autologous promoter is the **pertussis** **toxin** operon (TOXp) promoter and the Bordetella gene is selected from the group consisting of the filamentous haemagglutinin operon (FHA) and. . . promoter is the filamentous haemagglutinin operon (FHA) promoter and the Bordetella gene is selected from the group consisting of the **pertussis** **toxin** operon (TOX) and pertactin (PRN) gene.

12. . . . a Bordetella gene fused at the ATG start codon to an autologous Bordetella promoter, wherein: (1) said promoter is the **pertussis** **toxin** operon (TOXp) promoter and the Bordetella gene is selected from the group consisting of the filamentous haemagglutinin operon (FHA) and. . . said promoter is the filamentous haemagglutinin operon (FHAp) promoter and the Bordetella gene is selected from the group consisting of **pertussis** **toxin** operon (TOX) and pertactin (PRN) gene; (b) introducing said hybrid gene into a Bordetella strain to form a viable transformed. . .

Trying 01083...Open

PLEASE ENTER HOST PORT ID:
PLEASE ENTER HOST PORT ID:x
LOGINID:d184geb
PASSWORD:
TERMINAL (ENTER 1, 2, 3, 4, OR ?): 3

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APR 28 1998 for U.S. Patent Image Data.

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* *
  *                W E L C O M E   T O   T H E                    *
*
  *          U. S.   P A T E N T   T E X T   F I L E              *
*
  * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
* *

=> s pertussis

L1         1133 PERTUSSIS

=> s toxin

L2         4029 TOXIN

=> s l1(5n)l2

L3          226 L1(5A)L2

=> s mutat? or substitut? or mutan? or mutagen?

          11102 MUTAT?
         402540 SUBSTITUT?
          11912 MUTAN?
           7771 MUTAGEN?
L4       411817 MUTAT? OR SUBSTITUT? OR MUTAN? OR MUTAGEN?

=> s repla?c

'?' TRUNCATION SYMBOL NOT VALID WITHIN 'REPLA?C'

=> s replac?

L5       572562 REPLAC?

=> s l4 or l5

L6       832228 L4 OR L5
 75% OF LIMIT FOR TOTAL ANSWERS REACHED

=> s l3(5n) l6

L7           14 L3(5A) L6

=> d
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1.  5,705,361, Jan. 6, 1998, Hybrid transposon with PT operon,
plasmids
and bacterial strains therefor; Mark Walker, et al., 435/69.3,
252.3,
320.1 [IMAGE AVAILABLE]

=> d kwic

US PAT NO:     5,705,361 [IMAGE AVAILABLE]              L7: 1
of 14

DETDESC:

DETD(10)

 In . . . and biological activities is a protective
antigen. Infect.
Immun. 58:3337-3347; and Nencioni, L., et al. 1990.
Characterization of
genetically inactivated **pertussis** **toxin** **mutants**:
candidates
for a new vaccine against whooping cough. Infect. Immun.
58:1308-1315).
However, those methods rely on the purification of detoxified.
. .

=> d fro

US PAT NO:     5,705,361 [IMAGE AVAILABLE]              L7: 1
of 14
DATE ISSUED:   Jan. 6, 1998
TITLE:         Hybrid transposon with PT operon, plasmids and
bacterial
                 strains therefor
INVENTOR:      Mark Walker, Brunswick, Federal Republic of
Germany
               Kenneth Timmis, Brunswick, Federal Republic of
Germany
ASSIGNEE:      Gesellschaft fur Biotechnologische Forschung
mbH GBF,
                 Brunswick, Federal Republic of Germany
(foreign corp.)
APPL-NO:       08/137,139
DATE FILED:    Oct. 21, 1993
PCT-FILED:     Apr. 24, 1992
PCT-NO:        PCT/EP92/00910
371-DATE:      Oct. 21, 1993
```

102(E)-DATE: Oct. 21, 1993
PCT-PUB-NO: WO92/19750
PCT-PUB-DATE: Nov. 12, 1992
FRN-PRIOR: Federal Republic of Germany41 13 385.4 Apr. 24, 1991
INT-CL: [6] C12P 21/02; C12N 1/20; C12N 15/74
US-CL-ISSUED: 435/69.3, 252.3, 320.1
US-CL-CURRENT: 435/69.3, 252.3, 320.1
SEARCH-FLD: 435/320.1, 252.3, 172.3, 69.3; 424/92
REF-CITED:

U.S. PATENT DOCUMENTS

4,883,761 11/1989 Keith et al. 435/320.1

OTHER PUBLICATIONS

Walker et al., Infection and Immunity, vol. 59, Nov. 1991, pp. 4238-4248.
Herrero et al., V. Bacteriol., vol. 172, Nov. 1990, pp. 6557-6567.
Bloom, Rev. Infect. Diseases, vol. 11, Supplement 2, 1989, pp. 5460-5466.
Knapp et al., vol. 170, J. Bacteriol., 1988, pp. 5059-5066.

ART-UNIT: 185
PRIM-EXMR: James S. Ketter
LEGAL-REP: Kane, Dalsimer, Sullivan, Kurucz, Levy, Eisele and Richard

ABSTRACT:

The invention relates to a hybrid transposon having a PT operon, to plasmids and to bacterial strains (hosts) therefor.

12 Claims, 4 Drawing Figures

=> d clm

US PAT NO: 5,705,361 [IMAGE AVAILABLE] L7: 1 of 14

CLAIMS:

CLMS(1)

We claim:

1. A plasmid for the stable expression of pertussis toxin in a bacterial microorganism which comprises;

a promoterless hybrid transposon wherein a transposase gene is arranged

outside of inverted repeats of the transposon; and

having a pertussis toxin operon inserted between the inverted repeats;

said inverted repeats being in shortened form, thereby permitting a

further transposition;

said plasmid permitting a stable insertion of the pertussis toxin operon

into a bvg-negative bacterial strain.

CLMS(2)

2. A plasmid according to claim 1 wherein the transposon is a mini-transposon.

CLMS(3)

3. A plasmid according to claim 1 wherein the transposon is from Tn5 and the inverted repeats each have a length of approximately 19 base pairs.

CLMS(4)

4. A plasmid according to claim 1 wherein the operon is selected from the group consisting of a wild-type operon and an operon that encodes a pertussis toxin modification effective against whooping cough.

CLMS(5)

5. A plasmid according to claim 1 wherein the hybrid transposon contains a kanamycin resistance gene.

CLMS(6)

6. A plasmid which is promotorless having the following features and is

a suicide vector that has a mini-transposon for pertussis toxin

expression for transcriptional fusions with native promoters, having

1. a mob site,

2. an ampicillin resistance gene and

3. in each case, 19 base pairs of the terminal Tn5 end which flank,

4. a kanamycin resistance gene and
5. a promotorless operon; and also having
6. a IS50.sub.R -transposase gene.

CLMS(7)

7. A bvg-negative bacterial strain containing a plasmid according to
claim 1.

CLMS(8)

8. The bacterial strain of claim 7 which is selected from the group
consisting of Bordetella pertussis, Bordetella parapertussis and
Bordetella bronchiseptica.

CLMS(9)

9. A bvg-negative bacterial strain wherein a pertussis toxin operon has
been incorporated by means of a plasmid according to one of claims 1, 2
and 3 to 6.

CLMS(10)

10. The strain of claim 9 selected from the group of species consisting
of Bordetella pertussis, Bordetella parapertussis and Bordetella
bronchiseptica.

CLMS(11)

11. The strain of claim 10 which is Bordetella bronchiseptica ATCC
10580.

CLMS(12)

12. A process for the stable expression of pertussis toxin which
comprises;
culturing a bvg-negative bacterial strain containing a plasmid according
to one of claims 1, 2 and 3 to 6.

=> s (arg or arginine)(w)9 or arg9 or arginine9

```
      8246 ARG
     13998 ARGININE
   1660508 9
        49 (ARG OR ARGININE)(W)9
         8 ARG9
         1 ARGININE9
L8      57 (ARG OR ARGININE)(W)9 OR ARG9 OR ARGININE9

=> s l8(p)l1

L9       1 L8(P)L1

=> s l3 and l8

L10      1 L3 AND L8

=> s vaccine

L11   4528 VACCINE

=> s l11(p)l3

L12     48 L11(P)L3

=> d 1-3
```

1. 5,725,860, Mar. 10, 1998, Method for reducing the risk of developing
diabetes; Robert Bartlett Elliott, 424/240.1; 514/2, 21 [IMAGE AVAILABLE]

2. 5,705,361, Jan. 6, 1998, Hybrid transposon with PT operon, plasmids
and bacterial strains therefor; Mark Walker, et al., 435/69.3, 252.3,
320.1 [IMAGE AVAILABLE]

3. 5,695,766, Dec. 9, 1997, Highly virulent porcine reproductive and
respiratory syndrome viruses which produce lesions in pigs and vaccines
that protect pigs against said syndrome; Prem S. Paul, et al., 424/204.1,
209.1, 218.1, 815; 435/235.1, 236, 237, 238, 239 [IMAGE AVAILABLE]

=> d kwic

US PAT NO: 5,725,860 [IMAGE AVAILABLE] L12: 1 of 48

DETDESC:

DETD(45)

The conclusions we draw from this are that the pertussis **vaccine** is the active adjuvant in the mixed, triple **vaccine**, and that the diphtheria and tetanus **vaccine** are without effect. It also appears that A-chain itself, or in combination with diphtheria and/or tetanus **vaccine** is ineffective. The pertussis **vaccine** used was a "cellular" **vaccine** containing many defined, and some undefined components, and so we are unable to specify which component or components of the **vaccine** contain(s) the active principle. Indeed, diphtheria and/or tetanus vaccines may be required in addition as "co-factors". It may be relevant that for a long time **pertussis** **toxin** has been known to stimulate insulin secretion from the islets of Langerhans, probably through the "G protein" control sequence.

=> d 2-3 kwic

US PAT NO: 5,705,361 [IMAGE AVAILABLE] L12: 2 of 48

SUMMARY:

BSUM(3)

The invention relates to a plasmid for bacterial expression of **pertussis** **toxin**, useful in **vaccine** preparation.

SUMMARY:

BSUM(5)

Increasing . . . has in turn resulted in an increase in the incidence of the disease. It is imperative that an effective, nonreactogenic **vaccine** of high acceptability be developed. Several potentially protective antigens are candidates for inclusion in a purified multi-component **vaccine**, including toxins, such as **pertussis** **toxin** (PT) and adenylate cyclase, and also several cell surface or secreted antigens like filamentous haemagglutinin and serotype-specific fimbriae (Robinson, A., et al. 1985. Pertussis **vaccine**: present status and future prospects. **Vaccine** 3:11-22; and Robinson. A., and L. A. E. Ashworth. 1988. Acellular and defined-component vaccines against pertussis, p. 399-417. In A.. . . is hampered by antigeni variation controlled by the bvg-positive regulatory locus (Gross, R., and R. Rappuoli. 1988. Positive regulation of **pertussis** **toxin** expression. Proc. Natl. Acad. Sci. 85:3913-3917; Knapp, S., and J. J. Mekalanos. 1988. Two trans-acting regulatory genes (vir and mod). . . E. coli under the control of the lambda P.sub.L promoter (Burnette, W. N., et al. 1988. Direct expression of Bordetella **pertussis** **toxin** subunits to high levels in Escherichia coli. Biotechnol. 6:699-706). The serotype 2 fimbrial sub-unit has also been expressed with the. . . also extremely unstable, being subject to both plasmid loss and gene deletions (Locht, C., et al. 1986. Molecular cloning of **pertussis** **toxin** genes. Nucl. Acids Res. 14:3251-3261).

DETDESC:

DETD(10)

In . . . that methods for the genetic detoxification of PT have recently been developed by several groups (Kimura, A., et al. 1990.

Pertussis **toxin** analog with reduced enzymatic and biological
activities is a protective antigen. Infect. Immun. 58:3337-3347; and
Nencioni, L., et al. 1990. Characterization of genetically inactivated
pertussis **toxin** mutants: candidates for a new **vaccine** against
whooping cough. Infect. Immun. 58:1308-1315). However, those methods rely
on the purification of detoxified PT from B. pertussis. The. . . of
bvg-negative strains of B. bronchiseptica in combination with methods for
the genetic detoxification of PT will lead to a **vaccine** component of
high purity and low reactogenicity.

US PAT NO: 5,695,766 [IMAGE AVAILABLE] L12: 3 of 48

DETDESC:

DETD(51)

The composition containing the present **vaccine** may be administered
in conjunction with an adjuvant. An adjuvant is a substance that
increases the immunological response to the present **vaccine** when
combined therewith. The adjuvant may be administered at the same time and
at the same site as the **vaccine** or at a different time, for example,
as a booster. Adjuvants also may advantageously be administered to the
animal in a manner or at a site or location different from the manner,
site or location in which the **vaccine** is administered. Adjuvants
include aluminum hydroxide, aluminum potassium sulfate, heat-labile or
heat-stable enterotoxin isolated from Escherichia coli, cholera toxin or
the B subunit thereof, diphtheria **toxin**, tetanus **toxin**,
pertussis **toxin**, Freund's incomplete adjuvant, Freund's complete
adjuvant, and the like. Toxin-based adjuvants, such as diphtheria
toxin, tetanus **toxin** and **pertussis** **toxin**, may be
inactivated prior to use, for example, by treatment with formaldehyde.

```
=> s (514/12 or 424/240.1 or 424/190.1 or 424/94.5)/ccls

          1716 514/12/CCLS
            45 424/240.1/CCLS
            80 424/190.1/CCLS
            61 424/94.5/CCLS
L13       1882 (514/12 OR 424/240.1 OR 424/190.1 OR
424/94.5)/CCLS

=> s l3 and l13

L14         47 L3 AND L13

=> d 1-3
```

1. 5,736,143, Apr. 7, 1998, Anti-inflammatory, tolerogenic and
immunoinhibiting properties of carbohydrate binding-peptides; Louis D.
Heerze, et al., **424/190.1**, 275.1; 514/885 [IMAGE AVAILABLE]

2. 5,731,151, Mar. 24, 1998, Regulator of contact-mediated hemolysin; C.
Harold King, et al., 435/6; **424/190.1**, 200.1, 248.1; 435/41, 69.1,
71.1; 536/25.3 [IMAGE AVAILABLE]

3. 5,725,860, Mar. 10, 1998, Method for reducing the risk developing
diabetes; Robert Bartlett Elliott, **424/240.1**; 514/2, 21 [IMAGE
AVAILABLE]

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=> s (toxin/clm) or holotoxin/clm or s1/clm

           724 TOXIN/CLM
             9 HOLOTOXIN/CLM
          1280 S1/CLM
L15       1997 (TOXIN/CLM) OR HOLOTOXIN/CLM OR S1/CLM

=> s l14 and l15
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L16          29 L14 AND L15

=> d his


     (FILE 'USPAT' ENTERED AT 13:58:18 ON 04 MAY 1998)
L1         1133 S PERTUSSIS
L2         4029 S TOXIN
L3          226 S L1(5N)L2
L4       411817 S MUTAT? OR SUBSTITUT? OR MUTAN? OR MUTAGEN?
L5       572562 S REPLAC?
L6       832228 S L4 OR L5
L7           14 S L3(5N) L6
L8           57 S (ARG OR ARGININE)(W)9 OR ARG9 OR ARGININE9
L9            1 S L8(P)L1
L10           1 S L3 AND L8
L11        4528 S VACCINE
L12          48 S L11(P)L3
L13        1882 S (514/12 OR 424/240.1 OR 424/190.1 OR
424/94.5)/CCLS
L14          47 S L3 AND L13
L15        1997 S (TOXIN/CLM) OR HOLOTOXIN/CLM OR S1/CLM
L16          29 S L14 AND L15

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ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y

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1998
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